REMARKS

Claims 1-26 are in the case. The Examiner is thanked for the interview with his SPE which took place on April 8, 2008. In the interview, it was suggested by the Examiner's SPE that evidence showing that prostaglandins, which are the subject of the cited DeLong et al. reference (US 2006/0247214) were not lipoxygenase inhibitors could be persuasive evidence towards a showing of patentability of the present claims.

In light of the suggestion made during the interview, Applicant submits herewith a true and accurate copy of pages 603 and 604 of Goodman and Gilman's *The Pharmacological Basis Of Theraputics*, Ninth Edition (Mcgraw-Hill 1996). There, it can be seen from the text and Figures 26-1 and 26-2, that prostaglandins do *not* serve as lipoxygenase inhibitors. In view of this corroboration of the Applicant's assertions during the interview, it is believed that the present claims are in a condition for allowance. If a declaration or anything further is required in order for the Examiner to fully consider the attached reference, it is requested that the Examiner contact the undersigned in this regard.

The Specification also has been amended herewith to overcome the Examiner's expressed concerns regarding proper trademark usage therein by capitalizing all discerned trademarks. Withdrawal of the prior objection to the Specification is respectfully requested.

The Claims also have been amended herewith to remove references to other treatable disorders beside the graying of scalp hair, without prejudice or disclaimer.

Favorable action on all of the pending claims is thus solicited. If any matter remains unresolved which may be resolved without the need for a formal action, the Examiner is invited to contact the undersigned.

Respectfully submitted,

/R. Andrew Patty II/
R. Andrew Patty II
Reg. No. 38,992
McGLINCHEY STAFFORD, PLLC
4703 Bluebonnet Blvd.
Baton Rouge, LA 70809
Telephone: (225) 291-4600
Facsimile: (225) 291-4606

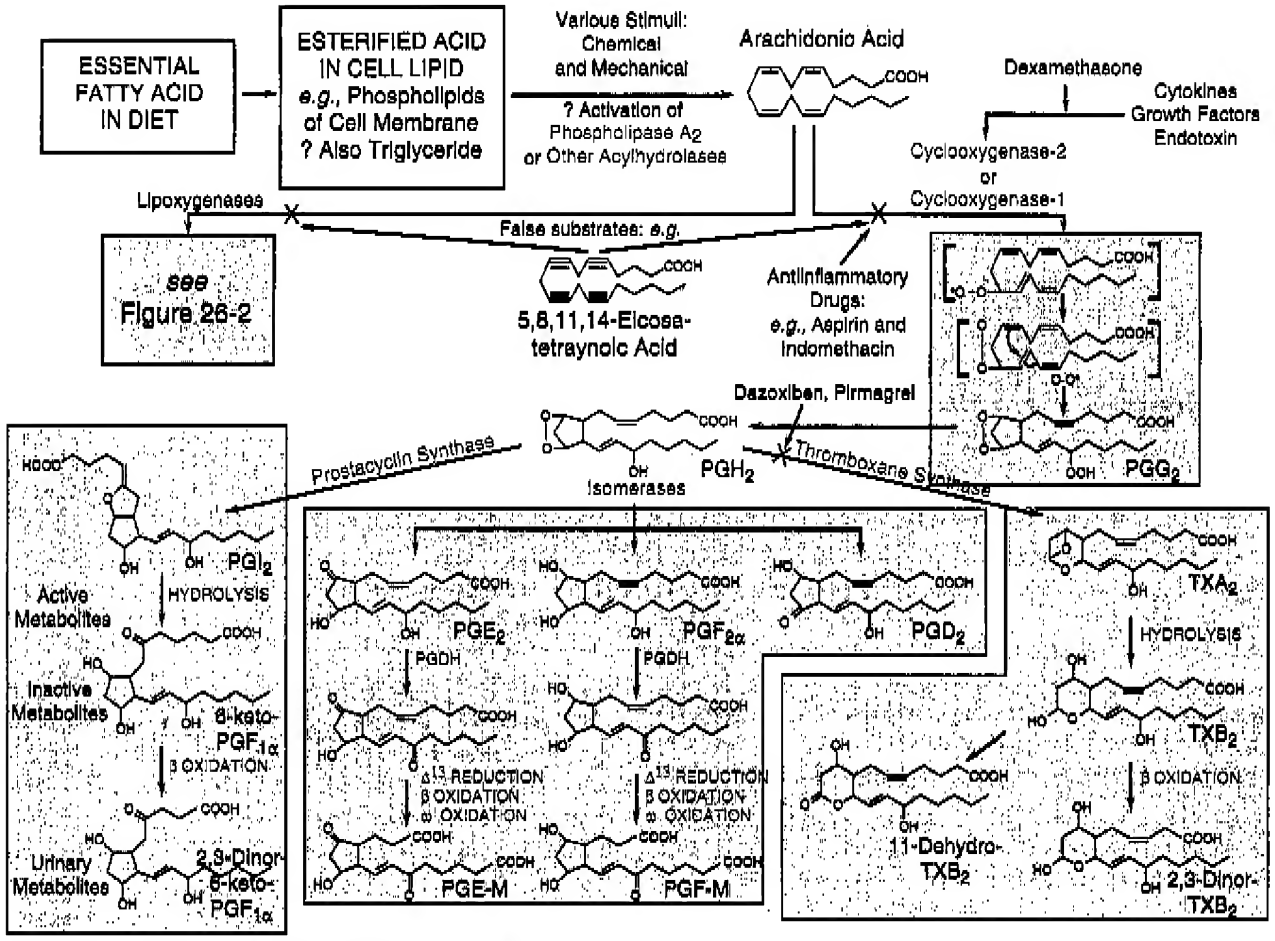

Figure 26–1. Biosynthesis of the products of arachidonic acid.

Two major routes of metabolism of arachidonic acid are shown. Lipoxygenase pathways lead to 12-HPETE, 12-HETE, 5-HPETE, and the leukotrienes (shown in Figure 26-2); the cyclooxygenase pathway leads to the cyclic endoperoxides (PGG and PGH) and the subsequent metabolic products (*see* text). Cyclooxygenase-1 (COX-1) is constitutively expressed. Cyclooxygenase-2 (COX-2) is induced by cytokines, growth factors, and endotoxin, an effect that is blocked by glucocorticoids. Compounds such as aspirin and indomethacin inhibit the cyclooxygenases but not the lipoxygenases, while 5,8,11,14, eicosatetraynoic acid inhibits both pathways. Dazoxiben and pirmagrel are selective inhibitors of thromboxane synthase. *See* text for abbreviations.

activating protein (*FLAP; see* Sigal, 1991). This binding activates the enzyme, results in its association with the cell membrane and increased synthesis of 5-HPETE and leukotrienes. An experimental drug, MK-886, inhibits the binding of 5-lipoxygenase to FLAP and reduces leukotriene synthesis. Leukotriene A (LTA) synthase is associated with 5-lipoxygenase and promotes the rearrangement of 5-HPETE to an unstable 5,6-epoxide, known as leukotriene A_4 (LTA_4) (Borgeat and Samuelsson, 1979); LTA_4 may be transformed by LTA hydrolase to a 5,12-dihydroxyeicosatetraenoic acid known as leukotriene B_4 (LTB_4); alternatively, it may be conjugated with glutathione by LTC_4 synthase to form LTC_4 (Murphy *et al.*, 1979). Leukotriene D_4 (LTD_4) is produced by the removal of glutamic acid from LTC_4, and LTE_4 results from the subsequent cleavage of glycine; the reincorporation of glutamic acid yields a γ-glutamylcysteinyl derivative called LTF_4 (*see* Samuelsson, 1983; Piper, 1984; Samuelsson *et al.*, 1987). It is now generally accepted that a mixture of LTC_4 and LTD_4 makes up the material originally known as the "slow-reacting substance of anaphylaxis" (SRS-A), first described by Feldberg and Kellaway (1938).

Products of Cytochrome P450. Arachidonate is metabolized to a variety of metabolites by enzymes that contain cytochrome P450 including 19- or 20-hydroxy arachidonate and epoxyeicosatrienoic acids, (*see* Fitzpatrick and Murphy, 1989). While these metabolites have vascular, endocrine, renal, and ocular effects, the physiological importance of this pathway remains to be clarified.

Other Pathways. Recently, a nonenzymatic pathway of arachidonate conversion has been discovered, giving rise to a novel series of agents termed *isoprostanes* (Morrow *et al.*, 1990). These compounds, while having stuctures similar to cyclooxygenase-derived PGs, arise *in vivo* from the free radical-catalyzed peroxidation of arachidonate independent of the cyclooxygenase. Unlike the cyclooxygenase-derived eicosanoids, the isoprostanes identified to date are formed

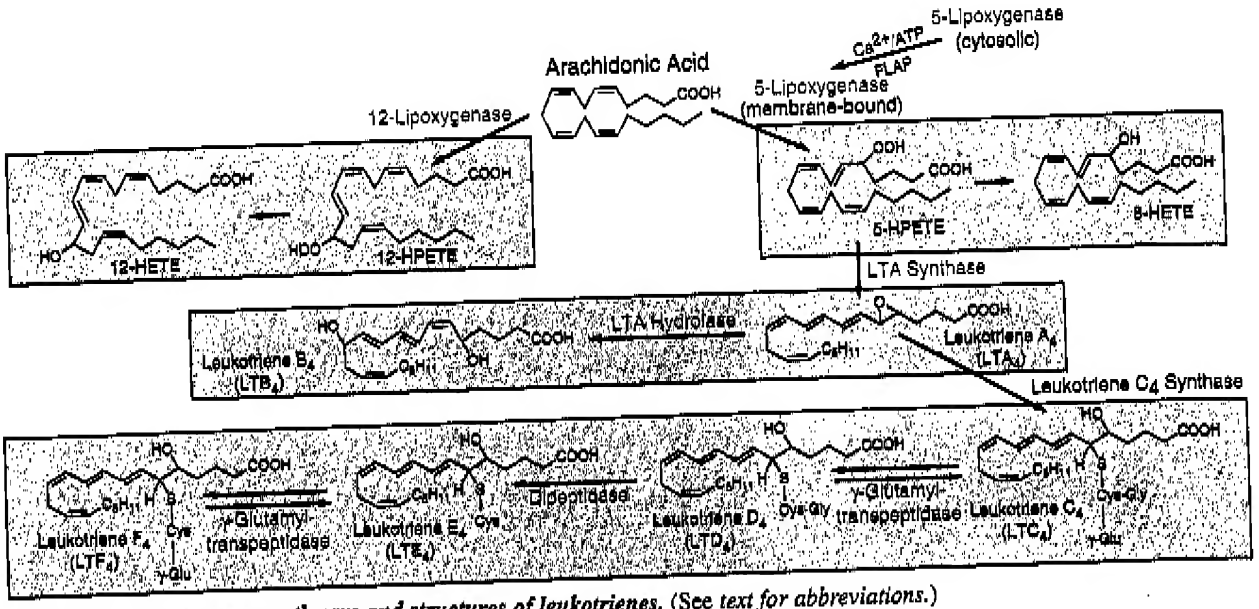

Figure 26–2. Lipoxygenase pathways and structures of leukotrienes. (See *text for abbreviations.*)

completely *in situ* on phospholipids and subsequently released preformed. Consequently, their production is not blocked by agents that suppress metabolism of free arachidonate, such as aspirin or nonsteroidal antiinflammatory agents, or by agents that suppress expression of the inducible COX-2 enzyme, or steroidal antiinflammatory agents. It is postulated that these agents might contribute to the pathophysiology of inflammatory responses insensitive to currently available steroidal or nonsteroidal antiinflammatory agents. Of importance is that this pathway of eicosanoid formation links free radical-mediated tissue injury with bioactive lipid-derived autacoid generation (Morrow *et al.*, 1990).

In the brain, arachidonate is coupled to ethanolamine to give arachidonylethanolamide, also called *anandamide* (Devane *et al.*, 1992). A similar reaction occurs with other unsaturated fatty acids. The reverse reaction is catalyzed by an N-acyl hydrolase. Anandamide binds to the cannabinoid receptor and displays all of the biochemical and behavioral effects of Δ^9-tetrahydrocannabinol, including inhibition of adenylyl cyclase, inhibition of L-type calcium channels, analgesia, and hypothermia. Anandamide may be an endogenous ligand for the cannabinoid receptor.

Inhibitors of Eicosanoid Biosynthesis. Many of the biosynthetic steps described above can be inhibited by drugs. Inhibition of phospholipase A_2 decreases the release of the precursor fatty acid and thus the synthesis of all metabolites derived therefrom. Since phospholipase A_2 is activated by Ca^{2+} and calmodulin, it may be inhibited by drugs that reduce the availability of Ca^{2+}. Glucocorticoids also inhibit phospholipase A_2, but they do so indirectly by inducing the synthesis of a protein (*lipocortin*) that inhibits the enzyme (Flower, 1990). Recent findings, however, indicate that COX-2 but not COX-1 expression is regulated by endogenous glucocorticoids (Masferrer, *et al.*, 1994); it is therefore possible that therapeutically effective doses of glucocorticoids as antiinflammatory agents correlate with their potency in suppressing cytokine-induced COX-2 expression rather than with their potency in inhibiting PLA_2.

Aspirin and related nonsteroidal antiinflammatory drugs originally were found to prevent the synthesis of prostaglandins from arachidonate in tissue homogenates (Vane, 1971). It is now known that these drugs inhibit cyclooxygenase and, as a result, inhibit the synthesis of PGG_2, PGH_2, and all that flows therefrom. However, these drugs do not inhibit the metabolism of arachidonate by lipoxygenases. In fact, inhibition of cyclooxygenase may lead to increased formation of leukotrienes, perhaps by increasing the amount of arachidonate that is available to the lipoxygenases (*see* Piper, 1984). Inhibition of cyclooxygenase provides an important basis for understanding many of the therapeutic and other effects of these agents (*see* Chapter 27).

COX-1 and -2 differ in their sensitivity to inhibition by certain antiinflammatory drugs (*see* Smith, 1992). Selective inhibition of COX-2 may be of therapeutic advantage, since this isozyme is probably involved in prostaglandin production at the site of inflammation but not at other sites such as the gastrointestinal tract and kidney. Thus, an inhibitor of COX-2 may be antiinflammatory without the side effects of reducing renal function or producing gastric ulcerations.

Since different metabolites of PGH_2 sometimes produce opposite biological effects (*see* below), there should be advantages in the development of compounds that preferentially inhibit one or another of the enzymes that metabolize PGH_2 (*see* Moncada and Vane, 1979). For example, there is current interest in drugs such as *dazoxiben*, and